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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,931	12/31/2003	Dilip G. Saoji	U 013963-9	6678

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EXAMINER	
JOHNSEN, JASON H	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 02/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/749,931	SAOJI ET AL.	
	Examiner	Art Unit	
	Jason H. Johnsen	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14,15 and 22-35* is/are rejected.

7)☒ Claim(s) *13,16-21,25,28 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) filed on 12/31/02.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 7/02/2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner is considering the information disclosure statements.

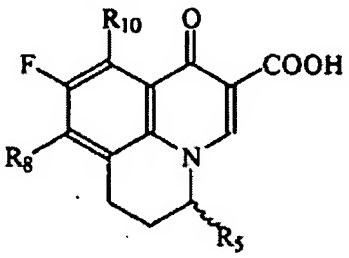
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-10, 12, 14, 15, 22, 24, 26, 27, and 30-34 are rejected under 35 U.S.C. 102(e) as being anticipated by Souza et al. (US 6,514,986).

Claim 1 discloses a pharmaceutical composition comprising an aqueous carrier having in solution therein a benzoquinolizine-2-carboxylic acid antimicrobial drug or salt and a pharmaceutically acceptable solubilizing agent selected from a basic amino acid, a cyclodextrin, a cyclodextrin polymer or derivative thereof or a mixture thereof. Claims 2 and 3 further limit the composition of claim 1, wherein the composition is suitable for parenteral administration,

intravenous injection or infusion. Claims 4-6 further limit the composition of claim 1, wherein the concentration of the drug is about 1mg/ml to about 100 mg/ml, about 4 mg/ml to about 12 mg/ml, and about 5 mg/ml to about 9 mg/ml respectively. Claim 7 further limits the composition of claim 1, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is selected from a compound of formula II: 

, wherein the variables are further defined. Claim 8 further limits the composition of claim 7 by further defining the properties of the substituants at R_8, R_{10} and, with greater particularity, R_5 position. Claim 9 further limits the composition of claim 7 by defining specific embodiments of the drug of the composition, one of which is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid. Claim 10 further limits claim 9 by teaching the arginine salt of claim 9's composition. Claim 12 further limits the composition of claim 9 by specifically defining the drug to be is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid. Claim 14 further limits the composition of claim 14 by teaching the amino acid is selected from arginine, histidine, arginine acetate, arginine-glutamate, arginine monohydrochloride, histidine acetate, histidine acetate dehydrate, histidine monohydrochloride, histidine monohydrochloride, lysine, lysine acetate, lysine monohydrochloride, ornithine, tryptophan or salts thereof. Claim 15 further limits the composition of claim 14 by teaching the amino acid to comprise L-arginine. Claim 22 further limits the composition of claim 1 further comprising a pharmaceutically acceptable vehicle

comprising a modifying agent selected from acids, bases, inorganic basic salts, organic basic salts, buffering agents or mixtures thereof and/or an agent for adjusting osmolality in amounts whereby the solution is substantially isotonic. Claim 23 further limits the composition of claim 1, wherein the physical form is selected from a concentrate, lyophilisate, powder, solution, or suspension. Claim 24 is drawn to a method of treating and/or preventing a bacterial infection disease in a subject comprising administering to the subject a pharmaceutical composition of claim 1. Claim 26 further limits the method of claim 24 by defining the subject as a human or animal. Claim 27 further limits the method of claim 24 by specifically defining the benzoquinolizine-2-carboxylic acid as S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid arginine salt, or solvatomorphic or polymorphic forms thereof. Claim 30 further limits the method of claim 24, wherein the solubilizing agent is selected from the group consisting of amino acids, cyclodextrin polymers or their derivatives, or mixtures thereof. Claims 31 and 32 further limit the method of claim 24 by teaching the mode of administration to be intravenous injection, infusion, or parenterally. Claims 33-35 define a process for preparing the pharmaceutical composition comprising mixing the benzoquinolizine-2-caboxylic acid with a pharmaceutically acceptable vehicle comprising a solubilizing agent at a concentration effective to maintain the drug in solution at physiologically compatible pH; Claim 34 defines the solubilizing agent to be selected from amino acids, cyclodextrin polymers or their derivatives or mixtures thereof; Claim 35 defines the benzoquinolizine-2-carboxylic acid to be made, one of which is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid.

Souza et al. teach a pharmaceutical composition comprising an aqueous carrier having in solution therein a benzoquinolizine-2-carboxylic acid antimicrobial drug or salt and a pharmaceutically acceptable solubilizing agent selected from a basic amino acid suitable for parenteral administration or intravenous injections (column 2, lines 29-34; column 8, lines 23 and 47). Souza et al. also teach the concentration of the drug to be 1 mg/ml to about 40 mg/ml (column 5, lines 25-28). Souza et al. specifically teach S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid and its arginine salt, including L-arginine (column 6, lines 44-50; column 4, lines 39-40). Souza et al. teach a modifying agent selected form acids, bases, organic basic salts and buffering agents (see example 1 and 2, column 9; claim 16, column 12). Souza et al. teach a method for treating a bacterial infection disease comprising administering to the subject, an animal or human, a pharmaceutical composition consisting of a benzoquinolizine-2-carboxylic acid antimicrobial drug, specifically, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid or salt, and a pharmaceutically acceptable solubilizing agent selected from a basic amino acid (claim 17, column 12), suitable for parenteral administration or intravenous injections (column 8, lines 23 and 47), that is in a physical form selected from suspensions, solutions or powders (column 8, lines 35-38). Souza et al. teach a process for preparing the pharmaceutical composition comprising mixing the benzoquinolizine-2-caboxylic acid, specifically S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid, with a pharmaceutically acceptable vehicle comprising a solubilizing agent, an amino acid, at a concentration effective to maintain the drug in solution at physiologically compatible pH (claim 13-16, column 12).

Claims 11 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Souza et al. (US 2002/0177559). Claim 11 discloses the composition of claim 9, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid 0.2 hydrate. Claim 12 further limits the composition of claim 9, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid.

Souza et al. teach S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid 0.2 hydrate (page 28, example 21) and S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid (page 9, paragraph 168).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4, 5, 7, 8, 9, 23, 24, 26, 27, and 30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Schulz et al. (US 2003/0045544). The limitations of these claims are discussed *supra*. Shulz et al. teach a composition comprising a benzoquinolizine-2-carboxylic acid drug, the genus of applicant's drug (page 3, paragraph 18 and 19), and one specific embodiment--9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo(i,j)quinolizine-2-carboxylic acid (page 5, paragraph 32). A genus renders obvious a species. Shulz et al. also teach the above-mentioned drugs corresponding hydrates, compatible acid addition salts (page 3, paragraph 22), solubilizers (page 10, paragraph 80) and a cyclodextrin (page 10, paragraph 80) for the purpose of treatment of bacterial diseases (page 5, paragraph 34). Shulz et al. also teach the drug in concentrations of .005 mg/ml to 200mg/ml, preferably from 10 to 100 mg/ml (page 6, paragraph 44), administered in the form of powders, solutions or suspensions (page 2, paragraph 10; page 18, claim 27), to humans and animals (page 2, paragraph 11).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the above taught composition for the purpose of treating bacterial infections having the above-cited reference before him. Although not explicitly claimed, one interested in creating a composition comprising benzoquinolizine-2-carboxylic acid drug and a solubilizing agent such as cyclodextrin for the purpose of treating bacterial diseases, would have ample guidance from Shulz et al. to create such a composition with a reasonable expectation of success. Shulz et al. contemplates the use of each component of applicant's composition enumerated in the claims above for the very purpose contemplated by applicant, ie to treat a bacterial infection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance

must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) There is no direction in the specification concerning produgs. c) There are no working examples for a prodrug of a compound of formula II. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body.. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula

of claim 1 as well as the presently unknown list potential prodrug derivatives embraced by claim 1. Thus, undue experimentation will be required to determine if any particular benzoquinolizine-2-carboxylic acid is, in fact, a prodrug.

Nowhere in the specification are directions given for preparing the "prodrugs" of the claimed compound. Since the structures of these "prodrugs" are uncertain, direction for their preparation must also be unclear. Directions to a team of synthetic pharmaceutical chemists and metabolism experts of how to search for a "prodrug" hardly constitute instructions to the BS process chemist of how to make such a compound.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7, 8, 24, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7, which includes the limitation of "pseudopolymorph" is indefinite. In the absence of the identity of moieties that are intended to provide representation of a pseudopolymorph and thus modify the instantly claimed chemical core, the identity of the "pseudopolymorph" moieties applicant intends as the invention would be difficult to ascertain. In the absence of said moieties, this claim containing the term "pseudopolymorph" is not described sufficiently to distinctly point out that which applicant intends as the invention. Applicants should include the moieties that are intended to effectuate substitution into the claims wherein said moieties are supported in the specification as originally filed.

Claim 8 is indefinite because it refers to "the formula (I)" of claim 7, when in fact there is not formula (I) found in claim 7. There is insufficient antecedent basis for this limitation in the claim. Claim 30 is indefinite because it refers to "said solubilizing agent" in claim 24, when in fact there is no "solubilizing agent" mentioned in claim 24.

Claim 24 is indefinite because it refers to "treating **and/or** preventing..." This language is ambiguous and indefinite in this context because if a method "prevents" a disease it cannot subsequently "treat" the disease as well.

Claims 8-12, and 25-32, which rely on claim 8 and claim 24 respectively, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims which depend from an indefinite claim are also indefinite. Ex parte Cordova, 10 U.S.P.Q.2d 1949, 1952 (P.T.O. Bd. App. 1989).

Claim Objections

Claims 13, 16, 17, 18, 18, 20, 21, 25, 28, and 29 are objected to as being dependent upon a rejected base claim.

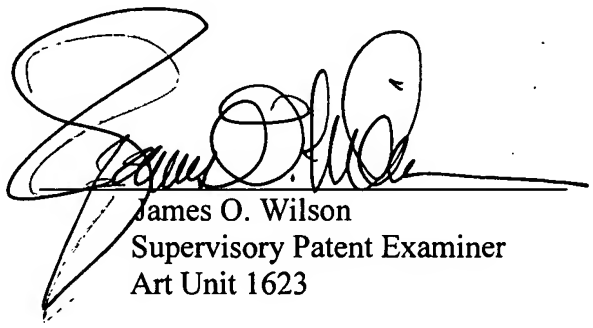
Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason H. Johnsen** whose telephone number is **571-272-3106.** The examiner can normally be reached on Mon-Friday, 8:30-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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